

Chart III contains a third curve, not present in the other charts, representing the tuberculosis mortality at different decades in comparison to the total mortality from all diseases at corresponding decades.

Chart IV indicates the prevalence of tuberculosis in Pennsylvania at different ages, the mortality actually increasing in the decade seventy to seventy-nine. The figures given by Cornet indicate that for every 10,000 males between sixty and seventy years of age as many as 99.65 die of tuberculosis. German statistics frequently give a relatively higher mortality from tuberculosis among the aged than do the English figures.

Smaller divisions of the age-periods than decades will often furnish more important information. Thus we find for the registration area of the United States for pneumonia (all forms) 147.3 persons die under one year of age per 10,000 persons alive at this age, while the mortality at four years is only 6.7 per 10,000. Again, the mortality for diarrhea and enteritis under one year is 345.7 per 10,000 and at four years only 2.5 per 10,000.

Much more could be said on this subject, but I trust the one point it seemed worth while to specially emphasize has been made plain, that no figures satisfactorily express the frequency of the deaths from any disease at a given age unless they show the number of deaths from the disease for every 10,000 persons living at the same age.

CONCERNING THE PRESENCE OF TUBERCLE BACILLI IN THE BLOOD OF TUBERCULOUS PATIENTS.¹

BY LEO KESSEL, M.D.,

NEW YORK CITY.

THE results of numerous studies of this subject during the past ten years have shown a complete lack of agreement among the various investigators. Some authors claim to have demonstrated tubercle bacilli regularly by a direct microscopic examination of the blood of tuberculous patients and frequently by the inoculation of such blood into guinea-pigs and rabbits, while other workers in this field report constantly negative results when microscopic examinations were made and few or no positive results when animal inoculations were employed. A review of the earlier work has been given by Bergeron,² and the more recent literature was well reviewed by Ernest Fraenkel,³ and in this country by Berry.⁴ That tubercle

¹ This work was carried out in the wards and laboratories of the Montefiore Home and Hospital for Chronic Diseases.

² Etude critique sur la presence du bacille de Koch dans le sang, Thèse, Paris, 1904.

³ Schmidt's Jahrbucher, March, 1913, cccxvii, Hft. 2, 201.

⁴ Tubercle Bacilli in the Blood, Jour. Inf. Dis., 1914, xiv, 162.

bacilli are at times present in the blood in acute miliary tuberculosis was demonstrated by Weichselbaum,⁵ Lustig,⁶ Meisel,⁷ and others. The occasional presence of tubercles in the spleen, liver, kidneys, and other organs of patients who have died of chronic pulmonary tuberculosis indicates that at times tubercle bacilli gain access to the circulation. Weigert⁸ emphasized the fact that pulmonary tuberculosis in contrast to acute miliary tuberculosis was not to be considered a general infection, and his views were until recently regarded as a fundamental truth in the pathology of human tuberculosis.

During the past ten years many authors have claimed, upon the basis of their investigations, that in cases of chronic pulmonary tuberculosis, tubercle bacilli are often present in the blood even in the incipient stage of the disease (Kennerknecht,⁹ Kurashige,¹⁰ Jessen and Rabinowitsch,¹¹ and Liebermeister,¹² while others state that they have found the organism in the blood of clinically healthy persons (Suzuki and Takaki,¹³ Rumpf¹⁴). Kennerknecht and Kurashige insist upon the existence of a primary bacillemia in tuberculous infections.

In order to determine the presence of tubercle bacilli in the circulation, two main methods have been pursued. Those workers who have relied upon one of these—namely, the microscopic examination of the blood—have reported results varying from 0 per cent. to 100 per cent. positive findings. At first, simple blood smears or the inoscopic method of Jousset¹⁵ were employed for microscopic examination; then the antiform and the acetic acid method of blood examination (Staubli¹⁶), and finally the Schnitter¹⁷ method was

⁵ Tuberkelbacillen im Blute bei allgemeiner akuter miliar Tuberkulose, Wien. med. Wochenschr., 1884, No. 12, 334.

⁶ Ueber tuberkelbacillen im Blute bei an allgemeinen akuter miliar tuberkulose Erkrankten, Wien. med. Wochenschr., 1884, No. 48, 1430.

⁷ Vorkommen von Tuberkelbacillen im Blute bei allgemeinen akuten miliar tuberkulose, Wien. med. Wochenschr., 1884, No. 48, 1429.

⁸ Neue Mittheilungen über Pathogenie der acuten allgemeinen miliar Tuberkulose, Deut. med. Wochenschr., 1883, No. 24, 349.

⁹ Ueber das Vorkommen von Tuberkelbazillen im Strömenden Blut bei Kindern, Beiträge z. klin. d. Tuberkulose, 1912, xxiii, 265.

¹⁰ Ueber das Vorkommen des Tuberkel Bacillus im Strömenden Blut der Tuberkulosen, Zeitschr. f. Tuberk., 1911, xvii, Hft. 4, 347.

¹¹ Ueber das Vorkommen von Tuberkelbacillen im Kreisenden Blute und die praktische Bedeutung dieser Erscheinung, Deut. med. Wochenschr., 1910, No. 24, 1116-1118.

¹² Ueber "Secundare" Tuberkulose, Med. klin., 1912, No. 25, 1018-1022.

¹³ Ueber die Beziehung zwischen der von Pirquetschen Reaction und den Tuberkelbacillen im Blut, Centralbl. f. Bacteriol., Orig., 1911, lxi, 149.

¹⁴ Ueber das vorkommen von Tuberkelbacillen im Blutstrom, Münch. med. Wochenschr., 1912, No. 36, 1951.

¹⁵ Nouvelle Methode pour isoler le bacille de Koch des bumeurs de l'organisme, La semaine médicale, 1903, No. 3, 22.

¹⁶ Beiträge zum nachweis von Parasiten im Blut, Münch. med. Wochenschr., 1908, No. 50, 2601.

¹⁷ Nachweis u. Bedeutung der Tuberkelbacillen im Strömenden Blut, Deut. med. Wochenschr., 1909, No. 36, 1566.

generally adopted. There have been several modifications of this last method by various investigators; all, however, are fundamentally similar. The pitfalls encountered in the microscopic methods elaborated to determine the presence of tubercle bacilli in the blood are many, and so misleading as to cast doubt upon the reliability of the positive reports by microscopic examination. Thus, distilled and tap water have been found by Beitzke¹⁸ and Brem,¹⁹ respectively, to contain acid-fast organisms. The stroma of red-blood corpuscles, lecithin, and cholestrin are acid-fast, and may, as Maixner²⁰ has shown, be mistaken for tubercle bacilli. Flakes of fibrin (Kahn)²¹ and red-colored crystals (Lange and Lindemann)²² may similarly lead to error. Anyone who has examined antiformin blood sediment stained according to the Much method for granules will, we believe, readily grant that the definite identification of tubercle bacilli is difficult and that the possibility of error is considerable; and finally it has long been known that organisms other than the tubercle bacillus, existing in our environment, may be acid-fast and that saprophytic bacteria occasionally acquire an acid-resistant power.

The other method which has been employed is that of animal inoculation, and for this purpose the guinea-pig has been the animal commonly used. That this animal is susceptible to infection with tubercle bacilli is a well-established fact, and while some investigators who claim advantages for the microscopic method have stated that the guinea-pig is not sufficiently sensitive, it has been shown by Selter²³ that ten tubercle bacilli suffice to inoculate a guinea-pig successfully, and Fraenkel and Baumann²⁴ think that this can be accomplished with a single organism. In order to avoid the possibility of using guinea-pigs previously inoculated with tuberculosis a preliminary tuberculin test can be made. It is probably true that all guinea-pigs are not equally susceptible to tuberculous infection (Markl),²⁵ and that some possess protective substances against tubercle bacilli (Kraus and Hofer);²⁶ but in a large series of experiments this becomes a factor of minor importance. It has been urged that the results of animal inoculation were

¹⁸ Eine Fehlerquelle bei der Antiformin-methode, Berlin. klin. Wochenschr., 1910, No. 31, 1451.

¹⁹ Investigation of Blood for Tubercle Bacilli, Jour. Amer. Med. Assoc., 1909, liii, 909.

²⁰ Quoted in Zeitschr. f. Tuberculose, 1914, xxii, Hft. 3, 267.

²¹ Zum Nachweis der Tuberkelbazillen im Strömenden Blut, Münch. med. Wochenschr., 1913, No. 7, 345.

²² Ueber Tuberkelbacillen im Strömenden Blut, Centralbl. f. Bacteriol. Ref., 1913, 57 Beiheft, 285.

²³ Vortrag auf d. Niederrhein Ges. f. Natur u. Heilk., Bonn, July, 1913.

²⁴ Zeitschr. f. hyg. u. infections Krankh., 1913, lxxvi, Hft. 1.

²⁵ Beitrag zur Kenntnis der Nagana infection bei Meerschweinchen, Centralbl. f. Bacteriol, 1904, xxxvii, 530.

²⁶ Ueber auflösung von Tuberkelbacillen im Peritoneum gesunder u. tuberkulösen Meerschweinchen, Deut. med. Wochenschr., No. 26, 1227.

negated by the bactericidal action of the injected blood, but Anderson²⁷ was able to show that this bactericidal action if present was slight by adding a small amount of emulsion of tubercle bacilli to the citrated blood from one of his cases by inoculating a guinea-pig and readily producing tuberculosis. Moreover, Moewes²⁸ has shown that the bacillemia present in tuberculous guinea-pigs could be demonstrated by inoculating the blood of these animals into other guinea-pigs and producing tuberculosis, and Rautenberg²⁹ has performed similar experiments with monkeys.

The argument has been advanced that the many negative results with animal inoculation could be traced to the treatment of the blood with antiformin before inoculation; this, it was held, destroyed the tubercle bacilli or so diminished their virulence that the inoculated animal could successfully withstand the infection.

Unlenhuth³⁰ has shown that a tuberculous sputum would yield positive inoculation results even after twenty-four hours' treatment with 20 per cent. antiformin, and Seemann³¹ demonstrated that a 15 per cent. antiformin solution could not kill the tubercle bacilli in one hour. In view of these experiments, and considering the fact that, under ordinary circumstances, a clear solution is obtained by the antiformin method in twenty minutes to half an hour, it is unlikely that this method influences the virulence of the tubercle bacilli.

Our experiments were undertaken with the hope of determining whether a bacillemia existed in patients suffering from chronic pulmonary tuberculosis, and at the same time to confirm or disprove the value of the methods recently advocated for this purpose.

The methods which we pursued were as follows:

1. The blood taken from patients with advanced pulmonary tuberculosis was inoculated directly into the peritoneal cavities of guinea-pigs.

2. The blood from some of these patients was treated and examined microscopically.

3. The blood from tuberculous patients who had previously received an injection of tuberculin was inoculated intraperitoneally into guinea-pigs.

4. The blood was withdrawn from tuberculous patients who had previously received a tuberculin injection, and after removal of the serum intraperitoneal injections were made into guinea-pigs.

²⁷ Bull. No. 57 Public Health and Marine Hospital Service of the United States, September, 1909.

²⁸ Tuberkelbacillen im Blute, Deut. med. Wochenschr., 1914, No. 10, 491.

²⁹ Zur Frage der Bacillaemie bei Tuberkulose, Deut. med. Wochenschr., 1914, No. 10, 492.

³⁰ Antiformin, Ein Bacterienauflösen des Desinfektionsmittel, Zentralbl. f. Bakt., 1908-1909, Abt. 1, Referate, xlii, 62.

³¹ Die Braubarkeit des antiformins zum Nachweis von Tuberkelbacillen, Berl. klin. Wochenschr., 1909, No. 14, 628.

5. The blood, after removal of the serum, was planted upon culture tubes of gentian-violet media.

The technique pursued was as follows:

Method 1. With aseptic precautions 5 c.c. of blood were withdrawn from a vein at the elbow into a syringe. The blood was immediately injected into the peritoneal cavity of a guinea-pig whose ventral surface had previously been shaved and treated with iodine. This direct and rapid transference of blood rendered the use of citrated solutions unnecessary; intraperitoneal injections were made because this route had yielded satisfactory results in the hands of other investigators. Blood withdrawn from thirty-eight patients was examined by this method. Tubercle bacilli were found in the sputum of thirty-seven of them, and in the remaining patient definite bilateral pulmonary signs were present. The patients were classified according to the classification adopted by the Association for the Study and Prevention of Tuberculosis. One patient was in stage I, seven patients were in stage II, and thirty were in stage III, and of the last mentioned, many were acutely ill with high fever, chills, sweats, and the clinical manifestations of cavitation.

Of 38 guinea-pigs inoculated in the manner described above, 2 died forty-seven days, 1 fifty-eight days, 1 sixty-six, and 1 eighty-three days following the injection, and were autopsied. The remaining 33 animals were chloroformed at periods varying from sixty-three to one hundred and twenty-nine days following the inoculation. Careful autopsies were also performed upon each of these animals, and material was taken from the lungs, liver, spleen, and kidneys for microscopic examination.

The autopsies and microscopic examination failed to reveal the slightest evidence of tuberculosis in the inoculated guinea-pigs. In none of the animals was there any enlargement of either the mesenteric or retroperitoneal lymph glands, so that the occurrence of a mild tuberculous infection from which the guinea-pig recovered cannot here be considered as even remotely possible.

Method 2. The blood of ten patients (Nos. 19, 20, 21, 22, 23, 24, 31, 32, 33, 34) in whom the disease was far advanced was withdrawn for microscopic examination. The method of treating the blood was exactly the same as that employed and advocated by Klemperer,³² and by which he had obtained positive results. Five c.c. of blood were withdrawn with aseptic precautions by a sterilized syringe which had been washed with distilled water. The blood was then transferred to a vessel which had been cleaned with soap suds, alcohol, and ether, cotton plugged and sterilized at 180° to 200° F. for one hour. To this 5 c.c. of blood, 10 c.c. of 3 per cent. acetic acid, prepared with distilled water, were added,

³² Tuberclebacillen im Blut, Zeitschr. f. klin. Med., 1914, clxxx, Hft. H. 2.

the vessel being carefully shaken, without producing foam and then allowed to stand half an hour. This solution was poured into two centrifuge tubes, which had been cleaned in a similar fashion to the first used vessel, and were passed through a flame just before being used, and centrifuged for half an hour. The supernatant fluid was taken off and five times the quantity of 33 per cent. antiformin added. The centrifuge tubes were closed with sterile rubber corks and shaken until the fluid became clear. Then the tubes were filled with double distilled water and centrifuged for one hour (2500 revolutions to the minute). A small white sediment remained; the supernatant fluid was removed, the sediment washed with double distilled water, and centrifuged for one and a quarter hours. This washing and centrifugalization were repeated four times. The sediment from each tube was finally poured onto two new slides. The slides had been washed in alcohol and sterilized at 250° F. for one hour and glowed over a Bunsen flame just before use. This preparation was placed in a sterile Petri dish and dried in an oven, and finally stained with a freshly prepared Ziehl-Nielsen stain. The stain was made up with distilled water. A careful systematic search was then made of the blood which had finally been deposited upon the two slides. At least four hours were devoted to the examination of each one of the slides from these ten cases. Not a single tubercle bacillus was found.

The negative results obtained with methods 1 and 2 induced us to attempt method 3, which concerns itself with the inoculation into guinea-pigs of blood from patients who had some hours previously received an injection of tuberculin. Such an injection of tuberculin has been followed, it has been stated, and then again denied, by a mobilization of tubercle bacilli in the circulation.

Bacmeister³³ inoculated the blood of fifteen patients, who had previously received a diagnostic tuberculin injection, into rabbits and produced tuberculosis in four instances. Mayer³⁴ studied sixteen tuberculous patients who had received tuberculin injections, but the blood from these patients inoculated into guinea-pigs failed to produce tuberculosis, while Liebermeister³⁵ obtained positive inoculation results after a tuberculin injection where these had previously been negative. The latter has also seen a previously positive inoculation yield negative results following a tuberculin injection; he doubts whether tuberculin in the usually employed dosage can cause a mobilization of tubercle bacilli.

Rabinowitsch and Moewes³⁶ found more positive inoculation results in tuberculous guinea-pigs after a tuberculin injection than

³³ Des auftreten virulenter Tuberkelbacillen im Blut nach der diagnostischen Tuberculin Injection, Münch med. Wochenschr., 1913, No. 7, 343.

³⁴ Ueber das Vorkommen von Tuberkelbazillen im Strömenden Blut u. in der menschlichen Milch, Zeitschr. f. Tuberculose, 1913, xxi, Hft. 5.

³⁵ Sitzungsber. d. neiderrh. Gesells. f. Natur u. Heilk, Bonn, January 20, 1914.

³⁶ Sitzung. der Berliner med. Gesellsch., February, 1914.

before, while Hage³⁷ failed to obtain positive inoculation results in tuberculous guinea-pigs regardless of how irregularly or systematically the tuberculin had been administered.

Method 3. Seven patients (Nos. 36, 37, 38, 39, 40, 41, and 42), of whom five were in the third stage and two were in the second stage of the illness, were subjected to a tuberculin injection; 0.1 milligram or 0.2 milligram of Koch's therapeutic tuberculin was injected subcutaneously; seven hours later 5 c.c. of blood were withdrawn for direct inoculation into the peritoneal cavity of a guinea-pig. Of these seven guinea-pigs, one died on the thirty-eighth day following inoculation and was autopsied, while the others were chloroformed at periods ranging from sixty-seven to ninety-one days. After the inoculation, careful autopsies were performed and material taken from the various organs for microscopic examination. No evidence of tuberculosis was revealed by any of these sections.

Method 4. Three patients (Nos. 45, 46, and 47), of whom two were in stage III and one in stage II of the disease, were each injected with 0.2 milligram of Koch's therapeutic tuberculin. Seven hours later 5 c.c. of blood were withdrawn from each patient. In order to exclude the possible presence of any protective substances the serum was removed from this blood by centrifugalization and 0.5 per cent. sterile acetic acid added to the blood. The centrifuge tube was then closed with a sterile rubber cork, thoroughly shaken, and centrifuged. The resulting sediment was injected intraperitoneally into a guinea-pig. These three pigs were chloroformed seventy-four days after inoculation. Careful autopsies were performed and material taken from the various organs for microscopic examination. Of these three inoculations one (Case 45) yielded a positive result and extensive tuberculosis of the lungs, liver, spleen, and lymph glands were found.³⁸

Method 5. From each of five far-advanced cases 5 c.c. of blood were withdrawn, centrifuged, and the supernatant serum removed. The sediment was then treated with 0.5 per cent. sterile acetic acid and centrifuged. The resulting sediment was implanted upon ten culture tubes of gentian violet. No growth was obtained at the end of two weeks, on any of the tubes.³⁹

SUMMARY. A number of different methods have been employed by us to determine whether tubercle bacilli are present in the circulation of patients with advanced pulmonary tuberculosis.

³⁷ Ueber das Vorkommen von Tuberkelbacillen im Strömenden Blut beim tuberkulösen u. tuberkulinsierten meerschweinchen, Beitr. z. klin. d. Tuberk., 1914, xxxi, Hft. 1, 71.

³⁸ Further experiments along these lines are now in progress and will be the subject of a later report.

³⁹ I am indebted to Mr. Pertroff, of the laboratory at the Adirondack Cottage Sanitarium, for giving me the gentian-violet media.

1. Blood withdrawn from thirty-eight patients was inoculated intraperitoneally into guinea-pigs. Autopsies and microscopic sections two to three months later failed to reveal any evidence of tuberculosis.

2. Microscopic examination of the blood withdrawn from ten patients yielded negative results. The many sources of error in the microscopic examination of blood for tubercle bacilli have been pointed out.

3. The blood of seven patients previously subjected to a tuberculin injection was inoculated intraperitoneally into guinea-pigs. Autopsies and microscopic sections failed to reveal any evidence of tuberculosis.

4. In three patients who had previously received a tuberculin injection, blood was withdrawn and after removal of the serum was inoculated intraperitoneally into guinea-pigs. One of the pigs developed an extensive tuberculosis.

5. An attempt made to grow the tubercle bacilli directly from the blood proved unsuccessful.

DISCUSSION. The negative results yielded by these forty-seven cases do not prove conclusively that tubercle bacilli are never present in the circulation, but they strongly suggest that a bacillemia such as is present in other infectious diseases is at least uncommon in pulmonary tuberculosis even in advanced stages of the disease. It may be that from time to time tubercle bacilli are washed into the circulation from a pulmonary focus, and that they rapidly disappear from the blood. That such a rapid departure from the blood does occur, has been demonstrated in the case of rabbits in whom tubercle bacilli could no longer be recovered from the blood thirty minutes after their intravenous inoculation (Heymann and Otto).⁴⁰

When the blood of ten patients previously subjected to a tuberculin injection was inoculated into guinea-pigs, one of the animals presented a generalized tuberculosis at autopsy. It would be unwise to draw conclusions from one positive result, but the nine negative results coincide with our daily clinical experience, for if a therapeutic tuberculin injection could cause virulent tubercle bacilli to appear in the circulation the development of acute miliary tuberculosis would be a common occurrence. Nevertheless, the question of a possible mobilization of tubercle bacilli following diagnostic and therapeutic tuberculin inoculations deserves careful investigation.

I wish to take this opportunity to express thanks to the house staff and Dr. Felberbaum of the laboratory for willing aid in carrying out this work.

⁴⁰ Centralbl. f. bacterial Ref., 1913, lvii, 293.

CASE REPORTS.

CASE 1.—Stage II. Temperature ranged between 98.6° and 101.4° F. March 27, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 74.

The pig was chloroformed July 21, 1914, one hundred and sixteen days following inoculation. No gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal glands; microscopically, no evidence of tuberculosis.

CASE 2.—Stage III. Temperature ranged between 96° and 102.4° F. March 31, 1914: temperature, 99° F.; 5 c.c. of blood injected into guinea-pig No. 2.

The pig was chloroformed August 7, 1914, one hundred and twenty-nine days after inoculation. No macroscopic evidences of tuberculosis; retroperitoneal and mesenteric glands were not enlarged; microscopically no evidences of tuberculosis.

CASE 3.—Stage III. Temperature ranged between 98° and 104° F. April 7, 1914: temperature, 103.6° F.; 5 c.c. of blood injected into guinea-pig No. 18.

The pig was chloroformed July 24, 1914, one hundred and one days after inoculation. No macroscopic evidences of tuberculosis; microscopically all of the organs appear normal; no enlargement of mesenteric or retroperitoneal glands.

CASE 4.—Stage III. Temperature ranged between 97.6° to 103.4° F. April 10, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 11.

The pig was chloroformed August 7, 1914, one hundred and nineteen days after inoculation. There were a number of adhesions between the stomach and liver; no evidences of tuberculosis, either grossly or microscopically.

CASE 5.—Stage I. Temperature ranged between 98.2° and 101° F. April 24, 1914: temperature, 100.2° F.; 3 c.c. of blood injected into guinea-pig No. 4.

The pig was chloroformed August 7, 1914, one hundred and five days after inoculation. There are marked adhesions between the spleen and the stomach, also a few adhesions between the parietal peritoneum and intestines; no enlargement of mesenteric or retroperitoneal glands; no gross or microscopic evidences of tuberculosis in any organ.

CASE 6.—Stage II. Temperature ranged between 98.8° and 100.4° F. April 24, 1914: 5 c.c. of blood injected into guinea-pig No. 5.

The pig was chloroformed August 7, 1914, one hundred and five days after inoculation. No evidences of tuberculosis, either grossly or microscopically; no enlargement of mesenteric or retroperitoneal glands.

CASE 7.—Stage III. Temperature ranged between 98° and 101° F. April 28, 1914: 5 c.c. of blood injected into guinea-pig No. 6.

The pig died June 25, 1914, fifty-eight days following inoculation. No evidence of tuberculosis in any organ, either grossly or microscopically; retroperitoneal or mesenteric glands were not enlarged.

CASE 8.—Stage III. Temperature ranged between 97° and 103° F. April 28, 1914: temperature, 100.2° F.; 5 c.c. of blood injected into guinea-pig No. 9.

The pig was chloroformed August 7, 1914, one hundred and one days after inoculation. No evidence of tuberculosis in any organ, either grossly or microscopically; congestion of spleen.

CASE 9.—Stage III. Temperature ranged between 97° and 99.2° F. April 28, 1914: temperature, 98.6° F.; 5 c.c. of blood injected into guinea-pig No. 8.

The pig was chloroformed August 7, 1914, one hundred and one days after inoculation. No evidence of tuberculosis in any organ, either grossly or microscopically; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 10.—Stage III. Temperature ranged between 98° and 100° F. April 28, 1914: temperature, 98.8° F.; 5 c.c. of blood injected into guinea-pig No. 7.

The pig was chloroformed August 7, 1914, one hundred and ninety-one days after inoculation. Some adhesive peritonitis present between liver, stomach, and intestines; moderate perisplenitis; no enlargement of mesenteric or retroperitoneal glands. Microscopically all organs negative for tuberculosis.

CASE 11.—Stage III. Temperature ranged between 97° and 101° F. May 5, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 12.

The pig was chloroformed August 7, 1914, ninety-four days after inoculation. No evidence of tuberculosis in any organ either grossly or microscopically; mesenteric and retroperitoneal glands not enlarged.

CASE 12.—Stage II. Temperature ranged between 98.4° and 102° F. May 5, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 10.

The pig was chloroformed August 7, 1914, ninety-four days after inoculation. Congestion of lungs, otherwise organs negative; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically no evidences of tuberculosis.

CASE 13.—Stage III. Temperature ranged between 98° and 101.4° F. May 5, 1914: temperature, 99.4° F.; 5 c.c. of blood injected into guinea-pig No. 11.

The pig was chloroformed August 7, 1914, ninety-four days after inoculation. No gross changes found; no enlargement of

mesenteric or retroperitoneal lymph glands. Microscopically no evidence of tuberculosis.

CASE 14.—Stage II.—Temperature ranged between 98° and 101° F. May 5, 1914: 5 c.c. of blood injected into guinea-pig No. 85.

The pig was chloroformed August 11, 1914, ninety-eight days after inoculation. Spleen somewhat enlarged, otherwise organs appear normal; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically no evidences of tuberculosis in any organ.

CASE 15.—Stage III. Temperature ranged between 97.8° and 100° F. May 6, 1914: temperature, 99.6° F.; 5 c.c. of blood injected into guinea-pig No. 56.

The pig was chloroformed August 11, 1914, ninety-seven days after inoculation. No gross or microscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal glands.

CASE 16.—Stage II. Temperature ranged between 97° and 101.4° F. May 6, 1914: temperature, 98.2° F.; 5 c.c. of blood injected into guinea-pig No. 15.

The pig was chloroformed August 11, 1914, ninety-seven days after inoculation. Spleen not enlarged, a grayish nodule on the surface microscopically shown to be inflammatory in character, other organs negative for tuberculosis, grossly and microscopically; no enlargement of peritoneal lymph glands.

CASE 17.—Stage II. Temperature ranged between 98° and 100.2° F. May 6, 1914: temperature, 99° F.; 5 c.c. of blood injected into guinea-pig No. 16.

The pig died July 28, 1914, eighty-three days after inoculation. Extensive ulceration of back. No evidence of tuberculosis upon gross or microscopic examination; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 18.—Stage III. Temperature ranged between 97° and 101.2° F. May 6, 1914: temperature, 100° F.; 5 c.c. of blood injected into guinea-pig No. 17.

The pig was chloroformed August 11, 1914, ninety-seven days after inoculation. No evidence of tuberculosis upon gross or microscopic examination; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 19.—Stage III. Temperature ranged between 97.2° and 102° F. June 5, 1914: temperature, 100.2° F.; 5 c.c. of blood injected into guinea-pig No. 58.

The pig was chloroformed August 11, 1914, sixty-seven days after inoculation. No gross or microscopic evidence of tuberculosis in any organ; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 20.—Stage III. Temperature ranged between 97.4° and 102° F. June 6, 1914: temperature, 101° F.; 5 c.c. of blood injected into guinea-pig No. 57.

The pig was chloroformed August 11, 1914, sixty-six days after inoculation. No evidence of tuberculosis upon gross or microscopic examination; no enlargement of mesenteric or retroperitoneal glands.

CASE 21.—Stage III. Temperature ranged between 97° and 103.8° F. June 8, 1914: temperature, 100° F.; 5 c.c. of blood injected into guinea-pig No. 59.

The pig was chloroformed August 11, 1914, sixty-four days after inoculation. The spleen is very small and is adherent to stomach; no gross or microscopic evidence of tuberculosis; no enlargement of retroperitoneal or mesenteric glands.

CASE 22.—Stage III. Temperature ranged between 97° and 102.4° F. June 8, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 84.

The pig was chloroformed August 11, 1914, sixty-four days after inoculation. No gross or microscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 23.—Stage III. Temperature ranged between 97° and 100.8° F. June 9, 1914: temperature, 100.2° F.; 5 c.c. of blood injected into guinea-pig No. 61.

The pig died August 14, 1914, three days after delivery; sixty-six days after injection. Congestion of lungs, purulent peritonitis, cloudy swelling of viscera; no evidence of tuberculosis in any organ; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopic examination negative for tuberculosis.

CASE 24.—Stage III. Temperature ranged between 97.4° and 100.6° F. June 9, 1914: temperature, 98° F.; 5 c.c. of blood injected into guinea-pig No. 62.

The pig was chloroformed August 11, 1914, sixty-three days after inoculation. Spleen slightly enlarged; no evidence of tuberculosis in any organ upon microscopic examination; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 25.—Stage III. Temperature ranged between 98° and 101° F. June 9, 1914: temperature, 99.6° F.; 5 c.c. of blood injected into guinea-pig No. 64.

The pig was chloroformed August 15, 1914, sixty-seven days after inoculation. Spleen very much enlarged, weighs 5 grams; no gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically organs appear normal.

CASE 26.—Stage III. Temperature ranged between 98° and 102.4° F. June 9, 1914: temperature, 100.2° F.; 5 c.c. of blood injected into guinea-pig No. 65.

The pig died July 26, 1914, forty-seven days after inoculation. Purulent pericarditis; purulent inflammation of left lung; pneumonia in right lung; cloudy swelling of other viscera. Microscopically no evidence of tuberculosis.

CASE 27.—Stage III. Temperature ranged between 97.6° and 100.6° F. June 10, 1914: 5 c.c. of blood injected into guinea-pig No. 66.

The pig was chloroformed August 15, 1914, sixty-six days after inoculation. No gross or microscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 28.—Stage III. Temperature ranged between 97.6° and 102° F. June 9, 1914: temperature, 99.6° F.; 5 c.c. of blood injected into guinea-pig No. 67.

The pig died July 26, 1914, forty-seven days after inoculation. Patches of bronchopneumonia in left lung; purulent peritonitis; cloudy swelling of liver, spleen, and kidneys. Microscopically no evidences of tuberculosis.

CASE 29.—Stage III. Temperature ranged between 97° and 102° F. June 9, 1914: temperature, 100° F.; 5 c.c. of blood injected into guinea-pig No. 68.

August 15, 1914, sixty-seven days after inoculation, the pig was etherized. No evidence of tuberculosis upon gross examination. Microscopically the organs were normal.

CASE 30.—Stage III. Temperature ranged between 98° and 102.8° F. June 10, 1914: temperature, 100.8° F.; 5 c.c. of blood injected into guinea-pig No. 63.

The pig was etherized August 15, 1914, sixty-six days after inoculation. Few peritoneal adhesions, no glandular enlargement. Microscopically no evidence of tuberculosis.

CASE 31.—Stage III. Temperature ranged between 97.4° and 102° F. June 11, 1914: temperature, 99.4° F., 5 c.c. of blood injected into guinea-pig No. 69.

The pig was etherized August 15, 1914, sixty-five days after inoculation. No gross or microscopic evidence of tuberculosis; no enlargement of retroperitoneal or mesenteric lymph glands.

CASE 32.—Stage III. Temperature ranged between 97° and 102.4° F. June 11, 1914: temperature, 101° F.; 5 c.c. of blood injected into guinea-pig No. 70.

The pig was etherized August 15, 1914, sixty-five days after inoculation. No gross or microscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands.

CASE 33.—Stage III. Temperature ranged between 97° and 103.6° F. June 12, 1914: temperature 102° F.; 5 c.c. of blood injected into guinea-pig No. 71.

The pig died August 8, 1914, fifty-seven days after inoculation. Small cyst at lower pole of right kidney, otherwise negative; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically, negative.

CASE 34.—Stage III. Temperature ranged between 97.4° and 102° F. June 12, 1914: temperature, 99.4° F.; 5 c.c. of blood injected into guinea-pig No. 72.

August 15, 1914, the pig was etherized, sixty-four days after inoculation. No gross or microscopic evidence of tuberculosis.

CASE 35.—Stage II. Temperature ranged between 97° and 100° F. June 12, 1914: temperature, 98.8° F.; 5 c.c. of blood injected into guinea-pig No. 73.

August 15, 1914, the pig was etherized, sixty-four days after inoculation. No gross evidence of tuberculosis. Microscopically the organs were normal.

CASE 36.—Stage II. Temperature ranged between 97° and 101.6° F. June 19, 1914: Koch's therapeutic tuberculin 0.1 mgm. injected at 9 A.M. Temperature, 100.2° F.; 4.5 c.c. of blood injected into guinea-pig No. 75 at 4 P.M.

The pig was chloroformed September 18, 1914, ninety-one days after inoculation. No evidence of tuberculosis; mesenteric and retroperitoneal glands are not enlarged. Microscopically negative for tuberculosis.

CASE 37.—Stage III. Temperature ranged between 97° and 100° F. June 19, 1914: Koch's therapeutic tuberculin 0.1 mgm. injected at 9 A.M. Temperature, 99.2° F.; 2.5 c.c. of blood injected into guinea-pig No. 76 at 4 P.M.

The pig was chloroformed September 18, 1914, ninety-one days after inoculation. No evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically all the organs were normal.

CASE 38.—Stage III. Temperature ranged between 97° and 100° F. June 19, 1914: Koch's therapeutic tuberculin 0.1 mgm. injected at 9 A.M. Temperature, 99.2° F.; 5 c.c. of blood injected into guinea-pig No. 77 at 4 P.M.

The pig was chloroformed September 18, 1914, ninety-one days after inoculation. A few adhesions found between intestine and liver; spleen embedded in a mass of adhesions. Microscopically negative for tuberculosis.

CASE 39.—Stage III. Temperature ranged between 97° and 100.4° F. June 23, 1914: Koch's therapeutic tuberculin 0.2 mgm. injected at 9 A.M. Temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 81 at 4 P.M.

The pig was chloroformed September 18, 1914, eighty-seven days after inoculation. No gross evidences of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically organs are negative.

CASE 40.—Stage II. Temperature ranged between 98° and 101.8° F. July 7, 1914: Koch's therapeutic tuberculin 0.2 mgm. injected at 9 A.M. Temperature, 101° F.; 5 c.c. of blood injected into guinea-pig No. 78 at 4 P.M.

The pig was chloroformed September 18, 1914, seventy-three days after inoculation. No gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically all the organs are negative.

CASE 41.—Stage III. Temperature ranged between 98° and 100.4° F. July 13, 1914: Koch's therapeutic tuberculin 0.2 mg. injected at 9 A.M.; 5 c.c. of blood injected into guinea-pig No. 79 at 4 P.M.

The pig died August 20, 1914, thirty-eight days after inoculation. No gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically all the organs are negative.

CASE 42.—Stage III. Temperature ranged between 98° and 100.6° F. July 13, 1914: Koch's therapeutic tuberculin 0.1 mg. injected at 9 A.M. Temperature, 99.6° F.; 5 c.c. of blood injected into guinea-pig No. 82 at 4 P.M.

The pig was chloroformed September 18, 1914, sixty-seven days after inoculation. No gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically all the organs are negative.

CASE 43.—Stage III. Temperature ranged between 98° and 104° F. July 21, 1914: temperature, 103° F.; 2.5 c.c. of blood injected into guinea-pig No. 83.

The pig was chloroformed September 18, 1914, fifty-nine days following inoculation. No gross evidence of tuberculosis; no glandular enlargement. Microscopically all the organs are negative.

CASE 44.—Stage III. Temperature ranged between 97° and 102° F. July 28, 1914: temperature, 99.2° F.; 4 c.c. of blood injected into guinea-pig No. 86.

October 13, 1914, seventy-seven days following inoculation, the pig was chloroformed; no microscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically the organs are negative.

CASE 45.—Stage II. August 1, 1914, 0.2 mg. of Koch's therapeutic tuberculin injected at 9 A.M. Temperature, 100.4° F.; seven hours after injection of tuberculin, 5 c.c. of blood withdrawn. Blood treated as described in text. Sediment injected into guinea-pig No. 89.

October 13, 1914 the pig was chloroformed, seventy-four days following inoculation. Tuberculosis of lungs, liver, spleen, and lymph glands. December 8: no apparent change in clinical condition of patient. No temperature changes followed above experiment.

CASE 46.—Stage III. Temperature ranged between 97° and 101.6° F. August 1, 1914, seven hours after injection of 0.2 mg. of Koch's therapeutic tuberculin, temperature, 99.4° F.; 5 c.c. of blood injected into guinea-pig No. 88. Blood treated as in Case 45.

The pig was chloroformed October 13, 1914, seventy-four days after inoculation. No gross evidence of tuberculosis. Microscopically all organs are negative.

CASE 47.—Stage III. Temperature ranged between 99° and 100.4° F. August 1, 1914, seven hours after inoculation with 0.2 mg. of Koch's therapeutic tuberculin, 5 c.c. of blood taken from patient and injected into guinea-pig No. 90. Blood treated as in Cases 45 and 46.

The pig was chloroformed October 13, 1914, seventy-four days after inoculation. No macroscopic evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically all the organs are negative.

CASE 48.—Stage III. Temperature ranged between 97° and 102.4° F. June 8, 1914: temperature, 100.4° F.; 5 c.c. of blood injected into guinea-pig No. 60.

The pig was chloroformed September 18, 1914, one hundred and two days after inoculation. No gross evidence of tuberculosis; no enlargement of mesenteric or retroperitoneal lymph glands. Microscopically no evidence of tuberculosis found.

PRURIGO NODULARIS AND LICHENIFICATION WITH TUMOR FORMATION.

BY CHARLES M. WILLIAMS, M.D.,

PROFESSOR OF DERMATOLOGY, UNIVERSITY OF VERMONT, BURLINGTON, VERMONT.

(From the Dermatological Department of the New York University (University and Bellevue), New York City.

ONE of the cases about to be described is from the service of Dr. Trimble, at the University and Bellevue Dermatological Clinic, and to him I am indebted for the privilege of recording it; the other is from the out-patient department of the Roosevelt Hospital. The case histories follow:

CASE I.—Mr. G. S., aged seventy-three years, a shoemaker, born in Germany. For the past eleven years he has suffered from moderate dyspnea on exertion, and he often has a cough in the early winter, but this is not serious. His bowels are regular, but sweet food is apt to start a mild diarrhea. He seldom suffers from headache. His general health was good until the spring of 1910, when he was taken sick rather suddenly with increased frequency of micturition, pain across the back, especially on the left side, which was tender to the touch, and stiffness of the muscles of the back. He was in bed for five weeks, and was told that he had kidney and stomach disease. There has been no return of these symptoms, but he has never been as well since, and is sleepy and tired most of the time.